Proposed Decision Memo for Insulin Pump: C-Peptide Levels as a Criterion for Use (CAG-00092R)

Decision Summary

CMS has determined that the evidence is adequate to conclude that continuous subcutaneous insulin infusion (CSII) is reasonable and necessary for treatment of diabetic patients: 1) who are documented (once) to either meet the updated fasting C-peptide testing requirement or be beta cell autoantibody positive; and 2) who satisfy the remaining criteria for insulin pump therapy detailed in the Medicare National Coverage Determinations Manual (Medicare NCD Manual 280.14, Section A.5).

CMS has determined that fasting C-peptide levels will only be considered valid with a documented, concurrently obtained fasting glucose $\leq$ 225 mg/dL. Insulinopenia may be documented by a fasting C-peptide level that is less than or equal to 110 percent of the lower limit of normal of the laboratory's measurement method. Alternatively, for patients with renal insufficiency and documented creatinine clearance (actual or calculated from age, weight and serum creatinine) $\leq$ 50 ml/minute, insulinopenia may be documented by a fasting C-peptide level that is less than or equal to 200 percent of the lower limit of normal of the laboratory's measurement method.

CMS will continue to allow coverage of all other uses of CSII in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201) or as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1).

CMS is requesting public comments on this proposed decision memorandum pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File CAG-00092R
Insulin Pump: C-Peptide Levels as a Criterion for Use

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SUBJECT: Proposed Coverage Decision Memorandum for C-Peptide Levels as a Criterion for Use of Insulin Pumps

DATE: September 30, 2004

I. Decision

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CMS is requesting public comments on this proposed decision memorandum pursuant to Section 731 of the Medicare Modernization Act.[1] After considering the public comments, we will issue a final decision memorandum.

II. Background

On April 1, 2004, CMS began a national coverage determination (NCD) for reconsideration of C-peptide levels as a criterion for use of insulin pumps in diabetic patients.

Diabetes is a disease in which insulin is absent or not functionally available in sufficient quantities to metabolic pathways including those for glucose utilization. Endogenous insulin, a hormone secreted by beta cells in the islets of Langerhans of the pancreas, is itself synthesized as a larger molecule called proinsulin that is subsequently cleaved into insulin and C-peptide. Serum C-peptide, measured by either radioimmunoassay or immunochemiluminometric assay techniques, is thus a marker for endogenous insulin release in diabetic patients.

Historically, diabetes has been broadly classified as type 1 diabetes mellitus (T1DM; formerly called type I, insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes) and type 2 diabetes mellitus (T2DM; formerly called type II, non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) with the distinguishing features largely based on clinical presentation. T1DM is generally associated with an earlier age of onset, thinner patients and ketosis, whereas T2DM is associated with a later age of onset and weight gain. T1DM accounts for 5 to 10% of diabetic patients and results from immune-mediated destruction of the pancreatic islet cells including pancreatic beta cells. T2DM accounts for 90 to 95% of diabetic patients and is generally characterized by insulin resistance. Grouped together to form a third etiologic classification are “other specific types” of diabetes mellitus, which include diabetic patients with genetic defects, diseases of the exocrine pancreas, endocrinopathies, drug-induced or chemical-induced diabetes, infections, uncommon forms of immune-mediated diabetes, and other genetic syndromes sometimes associated with diabetes.[2,3]

Our understanding about the etiology of diabetes continues to evolve and has complicated this diagnostic schema. Specifically, diabetes appears to be polygenic.[4] This is consistent with the observation that some patients cannot be classified as T1DM, T2DM or “other specific types” of diabetes, but are rather type 1.5 diabetes, late autoimmune diabetes in adults (LADA) or slowly progressive type 1 diabetes. Indeed, in the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetic patients, glutamic acid decarboxylase (GAD) antibodies - a marker and possibly causative antibody for type 1 diabetes - were noted to be present in a significant number of patients, albeit more prevalent in the cohort diagnosed between the ages of 25 and 35 years (34%) than in those diagnosed between the ages of 55 and 65 years (7%).[5,6] Takeda, *et al.’s* (2002) cross-sectional study (N = 4980 adult onset diabetic patients screened, N = 190 control without diabetes in first degree relatives) also identified such hybrid patients and further delineated markers associated with progression to insulin dependence.[7] GAD antibodies were detected in 188 (3.8%) screened patients and only 1 control. Of the patients with GAD antibodies and C-peptide data before and after a meal or after glucagon, 43% were considered insulin deficient and 57% were considered insulin sufficient. Certain haplotypes (HLA Class II genes), including the type 1 diabetes susceptibility alleles DRB1*0405 and DRB1*0901, were more common in the GAD positive-insulin deficient cohort than in controls. DRB1*0405 was more common in the GAD positive -insulin sufficient cohort than in controls. Putative protective genotypes DRB1*1502 and DQB1*0601 were more common in the GAD positive-insulin sufficient cohort than the GAD positive-insulin deficient cohort, but no more common than in controls. Insulinoma antigen (IA2) antibodies were more prevalent in the GAD positive cohort. GAD positive-insulin deficient patients were younger at the age of diagnosis and had lower maximal body mass indices and higher levels of GAD antibodies than GAD positive-insulin sufficient patients. 100% of GAD positive-insulin deficient patients used insulin whereas 38% of GAD positive-insulin sufficient patients were treated with insulin.

Two strategies for managing diabetic patients requiring insulin use either conventional or intensive insulin therapy; both strive to maintain blood glucose levels near the normal range. With conventional therapy, insulin replacement is provided by 1 to 2 subcutaneous injections of insulin daily, usually with a combination of short-acting and long-acting preparations. With intensive therapy, insulin replacement is provided by 3 to 5 multiple daily injections (MDI) of insulin or by CSII. CSII attempts to more closely replicate the normal pattern of secretion of endogenous insulin by supplying insulin at a baseline rate augmented by pre-meal insulin boluses. CSII delivery systems involve a battery-powered pump, which holds a reservoir of buffered regular insulin or approved short-acting insulin analog. The pump propels insulin from the reservoir through an infusion set into a catheter inserted in the subcutaneous tissue of the abdomen (or alternatively the thigh or hip). The CSII systems do not measure blood glucose levels or automatically adjust insulin delivery rates. For proper effect, the CSII user must measure blood glucose several times per day and program the pump to deliver an appropriate basal rate and pre-meal boluses of insulin. Because of these requirements, not all patients are candidates for intensive therapy.

CSII should be used only in diabetic patients who have been demonstrated to have T1DM or to be insulinopenic. With T1DM, most or all insulin producing capacity is lost within 12 months of presentation. C-peptide is typically low or absent in T1DM. With T2DM, insulin capacity may not be impaired initially. Patients typically have insulin resistance and can produce high levels of endogenous insulin, but the insulin is biologically less effective. The presence of this endogenous insulin permits therapies with various oral agents, which either cause more insulin to be released or improve the effectiveness of available insulin. Over time, however, the beta cells become exhausted, and oral agents become less effective.[8] This can be documented by a decrease in C-peptide during the fasted state or after a challenge by glucose, glucagon, Sustacal or a mixed meal.

Although C-peptide levels are useful for assessing beta cell reserve, there are important considerations to their use for these purposes. High glucose levels can cause glucose toxicity and impair both insulin and C-peptide release. This can be reversed with improved glycemic control. Renal dysfunction can also alter clearance of insulin and especially C-peptide. The effect on C-peptide levels appears most prominent when the creatinine clearance is < 50 ml/min. C-peptide levels may be artifactually high in this setting.[9]

In the absence, however, of a clear algorithm or diagnostic gold standard to separate the two major forms of diabetes, CMS chose in both prior NCDs for insulin pump therapy to utilize C-peptide testing as the best available method of measuring insulin secretory ability, assessing residual beta cell function and ensuring appropriate use of CSII.[10],[11] The current decision memorandum for reconsideration is an attempt to recognize and incorporate new data about the pathophysiology of diabetes and factors affecting C-peptide into a workable algorithm for Medicare beneficiaries.

III. History of Medicare Coverage

CMS's Center for Medicare Management (CMM) has determined that the subcutaneous insulin infusion pump falls within the benefit category set forth for "Durable Medical Equipment" in Section 1861(n) of the Social Security Act.

On August 26, 1999, HCFA (now CMS) issued the first decision memorandum (CAG-00041N) for “Continuous Subcutaneous Insulin Infusion Pumps” that utilized a C-peptide testing requirement for Medicare coverage of CSII pump therapy.[12]

On May 11, 2001, CMS issued a second decision memorandum (CAG-00092N) for “Insulin Pump: C-Peptide Levels as a Criterion for Use” and on January 1, 2002, revised the cut-point for the C-peptide testing requirement for Medicare coverage of CSII pump therapy.[13]

Coverage of CSII for the treatment of diabetic patientsin the home setting is currently defined by the criteria outlined in Section A.5 of Medicare NCD Manual 280.14.

On March 19, 2004, CMS received a request for reconsideration of the NCD for insulin pumps. In this letter Medtronic MiniMed requested removal of the C-peptide testing requirement as a condition of Medicare coverage for insulin pumps. The complete formal request letter is available on our tracking sheet at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=109.

IV. Timeline of Recent Activities

January 1, 2004	CMS began its modified NCD process on January 1, 2004. See "Changes to the National Coverage Determination Process" available electronically at http://www.cms.hhs.gov/coverage/8a4.asp
April 1, 2004	CMS accepted Medtronic MiniMed's formal request and initiated review. CMS also began, as of this posting date, its standard, initial 30-day comment period on this NCD to obtain public and scientific input relevant to the issue under consideration.
April 29, 2004	CMS teleconference with Office of Compliance in Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA) regarding history of past and present device recalls for insulin pumps.
July 9, 2004	Initial public comments posted to tracking sheet available electronically at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=109
July 13, 2004	CMS meeting with the American Association of Clinical Endocrinologists (AACE) Intensive Insulin Management Task Force and Medtronic MiniMed.

V. FDA Status

Medtronic MiniMed's 508 insulin infusion pump received 510(k) marketing approval as a class II device on August 18, 2000. Medtronic MiniMed's Paradigm insulin infusion pump received 510(k) marketing approval as a class II device on June 8, 1999. These pumps are indicated for use at set and variable rates for the management of diabetes mellitus in persons requiring insulin.

In an April 2004 teleconference with CMS, the FDA's Office of Compliance (OC) noted serious problems and recalls[14] involving Medtronic MiniMed's insulin pump products. CMS reviewed Medtronic MiniMed's regulatory history, which included several Class II and III recalls for potential timing problems, software lock-ups, development of pump case cracks and software errors in insulin infusion pumps. The OC reported that in October 2003, an FDA inspection revealed Medtronic MiniMed had conducted recall actions without the FDA's knowledge, and that in April 2004, the FDA had requested Medtronic MiniMed present a plan or procedure for alerting customers about new or changed products. In May 2004, Medtronic MiniMed issued a Class I recall of its Paradigm Quick-set Plus Insulin Administration Sets for potential leakage or interruption of insulin flow that could go unnoticed due to no accompanying alarm to alert users.[15] In May 2004, the FDA also initiated a full quality system inspection of Medtronic MiniMed due to the OC's serious concerns about recent adverse event reports and recalls. The OC suspected possible serious deviations from the Quality System Regulation and judged this inspection to be a critical assignment due to the life-saving nature of the device and Medtronic MiniMed's large share of the insulin infusion pump market. The OC additionally noted that other insulin pump manufacturers have experienced serious problems and recalls. This included a Class I recall of Disetronic's D-TRON insulin pump initiated in June 2002 for potential delivery of an unintended insulin bolus.[16]

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The overall objective for critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for Medicare patients. Evidence may consist of external technology assessments, internal review of published studies, recommendations from the Medicare Coverage Advisory Committee (MCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments. A fully detailed account of "General Methodological Principles of Study Design" that CMS staff utilizes to assess the relevant literature on the therapeutic or diagnostic item or service for specific conditions follows the conclusion and references for this decision memorandum (see Appendix A).

VII. Evidence

A. Introduction

This summary represents the body of evidence describing C-peptide levels and other laboratory measures as critical selection criteria for continued rational study and use of CSII pump therapy in diabetic Medicare patients. The health outcomes of interest to CMS include changes in the incidence of complications such as neuropathy, retinopathy, nephropathy or infection; the number of hypoglycemic or diabetic ketoacidotic episodes; and cardiovascular, non-cardiovascular or all-cause mortality.

In analyzing the evidence, CMS focused upon the following question: “Is there adequate evidence to further refine the criteria for a diagnosis of T1DM or insulinopenia sufficient to support the use of CSII in the Medicare population?"

B. Discussion of Evidence Reviewed

The evidence reviewed includes summaries of CMS’s 1999 and 2001 insulin pump decision memorandums, an external technology assessment, CMS’s internal technology assessment of new or reconsidered evidence, as well as professional society position statements and expert opinion.

1. Prior CMS Decision Memorandums for Insulin Pump Use

In the 1999 decision memorandum “Continuous Subcutaneous Insulin Infusion Pumps (CSII)” (CAG-00041N), CMS outlined the description and treatment of diabetes mellitus, reviewed the history of Medicare's coverage policies on diabetes management, analyzed the relevant scientific data related to the CSII pump, and delineated reasons supporting a positive national decision to cover the device for T1DM. The 1999 decision memorandum required physicians to document T1DM with a C-peptide level less than 0.5ng/ml for CSII coverage.[17]

In the 2001 decision memorandum for “Insulin Pump: C-Peptide Levels as a Criterion for Use” (CAG-00092N), CMS additionally discussed the use of C-peptide as a means to distinguish T1DM versus T2DM, reviewed the scientific and clinical literature on the use of C-peptide levels as a method of determining beta-cell activity, and delineated reasons for revising the C-peptide requirement for CSII pump therapy. The review of the scientific literature and subsequent discussions with clinicians, researchers and specialty groups formed the basis for CMS’s decision to initiate the C-peptide requirement as a reasonable method for distinguishing between T1DM and T2DM. The 2001 decision memorandum revised the cut-point for the C-peptide testing requirement to less than or equal to 110% of the lower limit of normal of the lab's measurement method.[18]

2. External Technology Assessment

CMS identified a 2003 National Institute for Clinical Excellence (NICE) technology appraisal on “Guidance on the Use of Continuous Insulin Infusion for Diabetes”.[19] NICE, an independent organization responsible for developing guidance documents for healthcare professionals and patients, is part of the United Kingdom National Health Service (NHS).

While not specifying diagnostic criteria, the NICE appraisal defined T1DM as follows: “In type 1 diabetes, the pancreas makes little or no insulin because the islet b cells, which produce insulin, have been destroyed through an autoimmune mechanism. Therefore, people with type 1 diabetes usually depend on daily insulin injections to survive.” (Section 2.2 of NICE guidance document)

In defining T2DM, the NICE appraisal wrote: “Type 2 diabetes results from failure of insulin production to overcome reduced tissue sensitivity to insulin (known as insulin resistance). Type 2 diabetes is a progressive disease in which insulin production declines as the disease progresses.” (Section 2.3 of NICE guidance document)

Guidance for T1DM

NICE recommended CSII as an option for T1DM provided that MDI therapy failed and that those receiving the treatment had the commitment and competence to effectively use CSII. (Section 1.1 of NICE guidance document)

Guidance for T2DM

The 2003 NICE technology appraisal noted that there was insufficient evidence with which to draw conclusions from studies comparing the effect of CSII with MDI treatment in T2DM. NICE concluded that CSII is not recommended for patients with T2DM requiring insulin therapy. (Section 1.6 of NICE guidance document)

3. Internal Technology Assessment

Literature Search

CMS extensively searched PubMed (1990 to present) for new randomized controlled trials (RCTs) and systematic reviews evaluating the use of clinical laboratory criteria to differentiate major types of diabetes and ensure appropriate use of CSII in patients with T1DM, T2DM and other specific types of diabetes requiring insulin. CMS likewise searched the Cochrane Collaboration, the NHS Centre for Reviews and Dissemination, and the INAHTA databases for all systematic reviews and technology assessments. Keywords used in CMS's search included C-peptide, diabetes, T1DM, T2DM, insulin pump, intensive insulin management and CSII. RCTs must have presented original data, included greater than or equal to 10 patients, examined health outcomes, and been published as full-length articles in peer-reviewed, English language journals. Uncontrolled studies and abstracts were excluded.

Summary of Evidence

Using the aforementioned search strategy to supplement the latest technology appraisal from NICE (2003), CMS identified 65 articles, 1 current health plan policy, 2 professional society position statements, 124 expert opinions from practitioners and 7 public comments from patients and family members. Articles subsequently reviewed have either been newly published since CMS's 2001 decision memorandum or are previously published relevant articles now being reconsidered or referenced for the first time.

Scientific Articles

Pickup, *et al.'s* (2002) meta-analysis studies performed between 1975 and 2000 identified 12 randomized controlled trials of insulin pump therapy compared with optimized insulin injection therapy for T1DM. This meta-analysis did not specifically define T1DM and also did not include trials of pregnant women or trials of newly diagnosed T1DM. All but Hanaire-Broutin's (2000) study were performed during the 1980s and were not part of CMS's literature search for new RCTs or systematic reviews of CSII. Outcome measures in Pickup's meta-analysis were glycemic control measured by mean blood glucose concentration and percentage of glycated hemoglobin, as well as total insulin dose. Glycemic control was slightly better during CSII compared with optimized injection therapy, including both a standardized mean blood glucose concentration difference of 0.56 (95% confidence interval of 0.35 to 0.77) equivalent to a difference of 1.0 mmol/l, and a lower percentage of glycated hemoglobin equivalent to a difference of 0.51%. CSII achieved this improved control with an average reduction of 14% in insulin dose equivalent to 7.58 units/day. Pickup and colleagues concluded the "difference in control between the two methods is small but should reduce the risk of microvascular complications."[20]

Weissberg-Benchell's (2003) meta-analysis of insulin pump therapy reported on 52 studies of T1DM, the majority of which were published before 1987. A total of 11 studies (1 with random assignment procedures) were classified as parallel group design comparing CSII pump therapy with MDI and conventional insulin therapy, and 41 studies (5 using random assignment and the remainder enrolling self-selected patients) were classified as paired design assessing the same patients before and after initiation of CSII. This study concluded that CSII was associated with improved glycemic control compared to MDI and conventional insulin therapy and did not appear to be associated with significant adverse outcomes. Weissberg-Benchell and colleagues, however, noted that the majority of studies in their meta-analysis were published before 1987 and that relatively few studies reported after the 1993 Diabetes Control and Complications Trial (DCCT) specifically examined the relative risks and benefits of CSII therapy. The authors recommended standardized and systematic reporting of outcomes data in future research and cautioned that their results "should not be viewed as a definitive statement about the efficacy of CSII therapy."[21]

The landmark DCCT (1993), which compared conventional and intensive insulin therapy, measured insulin dependence based on deficient C-peptide secretion of <0.2 pmol/ml and used this as a major patient eligibility criterion. Other major DCCT inclusion criteria included an age of 13 to 39 years; exclusion criteria included hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions. In this study of T1DM patients, the DCCT research group reported that intensive therapy administered either with three or more daily insulin injections or an external insulin pump effectively delayed the onset and slowed the progression of diabetic retinopathy, nephropathy and neuropathy (microvascular complications) in patients with insulin-dependent diabetes.[22,23]

Building upon the DCCT's original design, selection criteria and C-peptide testing protocol, the investigators subsequently published a 1998 DCCT follow-up study of annually measured stimulated C-peptide levels in a subgroup of patients it termed "responders". Among 855 of the 1441 DCCT participants who had T1DM for 1 to 5 years at baseline, 303 (35%) of those 855 patients were C-peptide "responders" defined as having a C-peptide level of 0.2 to 0.5 pmol/ml after ingestion of a standardized, mixed meal. Development of retinopathy, HbA1c levels and episodes of hypoglycemia were also measured. The results of the C-peptide screening during the feasibility phase of the DCCT provided insight into the natural history of residual beta cell function in T1DM, and this follow-up 1998 study showed responders receiving intensive therapy maintained a higher stimulated C-peptide level than those receiving conventional therapy. This 1998 analysis concluded that intensive therapy for T1DM helps sustain endogenous insulin secretion, which in turn was associated with improved metabolic control and decreased risk of hypoglycemia and chronic complications.[24]

In Hanaire-Broutin's (2000) randomized study of T1DM, inclusion criteria were HbA1c < 10%, negative C-peptide level and experience of intensified insulin therapy. A total of 41 C-peptide negative T1DM patients were studied to compare the efficacy of CSII versus MDI using the short-acting insulin lispro. In this unblinded crossover study comparing two successive periods of intensive insulin therapy by CSII and MDI, patients were randomly assigned to either CSII or MDI therapy for 4 months then switched to the other treatment for 4 months. Mean insulin dose and the frequency of hypoglycemic events were recorded. Hanaire-Broutin, *et al.* concluded that CSII pump therapy required lower doses of insulin lispro than MDI and did not increase the risk of hypoglycemia.[25]

In DeVries and colleagues' (2002) multicenter, open-label, double 16-week crossover trial of CSII (N = 39) and intensive insulin injection therapy (N = 40), inclusion criteria were T1DM patients between 18 and 70 years of age, with persistent poor control on three or more insulin injections a day, who were diagnosed at or before age 30 years, with a C-peptide level $\leq$ 0.2 nmol/l and glucose level $\geq$ 7.0 mmol/l.[26] In this study, CSII improved glycemic control and some aspects of health-related quality of life in patients with a history of long-term poor glycemic control.[27]

Linn, *et al.* (2003) also published the protocol for a study evaluating the effect of conventional versus intensive insulin therapy on residual beta cell function in T1DM, with anticipated three-year follow-up. In this ongoing study of newly diagnosed T1DM subjects, the presence of diabetes related antibodies were not mandatory for inclusion, but a negative C-peptide level at diagnosis is among the exclusion criteria. The authors noted that, while the bulk of uncontrolled trials in the past 20 years suggested that residual C-peptide might be beneficial for the prevention of diabetes related vascular disease, their trial will help settle whether preservation of residual insulin/C-peptide facilitates stable glucose levels.[28]

In patients with T2DM, a multicenter, randomized, parallel-group, 24-week study (N = 127) by Raskin and colleagues (2003) compared the efficacy, safety and patient satisfaction of CSII with MDI therapy. The study's inclusion criteria required that enrolled patients ≥ 35 years had at baseline a fasting C-peptide level > 0.2 nmol/l, BMI ≤ 43 kg/m^2 and HbA1c level ≥ 6% and ≤ 12%. Exclusion criteria were patients with impaired hepatic, renal or cardiac function, as well as recurrent hypoglycemia.[29] Raskin's study concluded that insulin aspart in CSII pump therapy showed efficacy and safety comparable to MDI for T2DM, and that patients with T2DM can be trained as outpatients to use CSII and prefer CSII to injections. As described by one of the study's co-authors (BB), a respondent in CMS's initial 30-day public comment period, the "main benefit in the CSII group of patients was improvement in quality of life and greater acceptance of intensive insulin therapy."

Five additional studies of CSII pump therapy examined by CMS for this reconsideration utilized inclusion or exclusion criteria other than a C-peptide level (see also Table 1). For example, in Jennings, *et al.'s* (1991) randomized trial to compare CSII (N = 10) with conventional insulin therapy consisting of twice daily regular and NPH insulin (N = 10) in T2DM patients poorly controlled on sulfonylureas, inclusion criteria included all Caucasian patients attending diabetes clinic, aged 40 to 65 years, without severe diabetic complications, who had previously been satisfactorily treated with sulfonylureas for at least 1 year. Patients were excluded if they had features of T1DM (including those with islet cell antibodies), retinopathy requiring laser therapy, serum creatinine > 200 µM, severe neuropathy, severe cardiovascular disease, an uncorrected endocrine abnormality, or another life-threatening disease. No additional definition of T1DM or specification of excluded T1DM patients was made. In this study of patients < 65 years of age without severe microvascular or macrovascular disease, the proportion of patients achieving satisfactory glycemic control was greater with CSII than conventional insulin therapy. Weight gain, insulin dosage and prevalence of hypoglycemia were similar in the two treatment groups.[30]

In Bode, *et al.'s* (1996) unblinded study comparing the incidence of severe hypoglycemia in T1DM patients (N = 55) crossed over from MDI to CSII, inclusion criteria included a minimum of 12 months on MDI before crossover and 12 months on CSII-based intensive therapy after crossover. These 55 patients were selected from "a population of 255 patients using CSII", and no other definition or specification of included T1DM patients was made. Criteria for switching from MDI to CSII included suboptimal glycemic control to intermediate-acting insulin, HbA1c > 8%, history of recurrent severe hypoglycemia, or hypoglycemic unawareness. In Bode's study, the incidence of severe hypoglycemia during MDI declined from 138 to 22 events per 100 patient-years during the first year of CSII (P < 0.0001) and remained significantly lower in years 2, 3 and 4 on CSII therapy. The difference in diabetic ketoacidosis rates between the MDI year and the CSII period (14.6 versus 7.2 events per 100 patient-years, respectively) was not statistically significant.[31]

In Boland, *et al.'s* (1999) nonrandomized study to evaluate psychosocial outcomes in adolescents with established T1DM utilizing CSII versus MDI, inclusion criteria included youths aged 12 to 20 years, with no other health problem except treated thyroid disease, treatment with insulin for ≥ 1 year, recent HbA1c between 7 – 14%, no more than two severe hypoglycemic events within the past 6 months, and in a school grade appropriate to within 1 year of their age. Patients were selected from a diabetes clinic caring for children, adolescents and young adults with T1DM. No other definition or specification of included T1DM patients was made. Data was reported on the first 75 patients enrolled in the study who completed 12 months of follow-up. Self-reported questionnaires demonstrated improvement in self-efficacy, depression and quality of life in both CSII and MDI treated patients.[32]

In Maniatis, *et al.'s* (2001) nonrandomized study (N = 56) to determine the feasibility and efficacy of CSII in routine pediatric diabetes care, inclusion criteria were HbA1c levels available ≥ 6months before and after CSII initiation, as well as duration of CSII ≥ 6 months. The children and adolescents selected were all cared for in a pediatric clinic for childhood diabetes, and no additional definition or specification of included T1DM patients was made. The mean duration of CSII therapy was 12.2 months (range: 6 – 35 months). Results for the entire cohort demonstrated a decrease in HbA1c from 8.5% to 8.3%, including 36 patients (64.3%) who maintained or achieved an HbA1c <8.0% or at least 1% lower than their pre-CSII level. Of concern were 10 of 17 patients with an initial HbA1c ≥ 9% who remained ≥ 9% on CSII, as well as 6 patients (10.7%) who demonstrated a clinically significant increase in HbA1c from 8.3% to 9.6% on CSII. Analysis of HbA1c subgroups could not identify any distinguishing features predictive of outcome on CSII, and Maniatis, *et al.* noted that additional study is underway to prospectively identify predictors for those at risk for metabolic deterioration on CSII therapy.[33]

In Tsui, *et al.'s* (2001) RCT to evaluate glycemic control, hypoglycemic events and quality of life in patients treated for 9 months with CSII (N = 13) versus MDI (N = 14), inclusion criteria included adults between 18 and 60 years of age with T1DM for >2 years, onset of diabetes on or before age 40, and ability to comply with treatment. Patients considered for inclusion in Tsui's trial had an "endocrine diagnosis of type 1 diabetes", but no other definition or specification of T1DM was stated for those selected. Patients were excluded if they had a history of more than two hypoglycemic episodes within the previous year; hemoglobinopathy; insulin resistance; extreme obesity (BMI >35 kg/m^2); severe late complications of diabetes; evidence of significant cardiovascular, hepatic disease, cancer, or cerebrovascular or severe peripheral vascular disease; or alcohol or drug abuse. In Tsui's study, no statistically significant differences in glycemic control, reported hypoglycemic events or quality of life were found.[34]

Table 1: Characteristics of Insulin Pump Studies

Study	Type	C-Peptide Inclusion Criterion	Age
DCCT Group (1993)	T1DM	<0.2 pmol/ml	13 to 39 years
Bode, *et al.* (1996)	T1DM	None	39.2 ± 12.9
DCCT Group (1998)	T1DM	0.2 to 0.5 pmol/ml	13 to 39 years
Boland, *et al.* (1999)	T1DM	None	12 to 20 years
Hanaire-Broutin, *et al.* (2000)	T1DM	Negative C-peptide	21 to 65 years
Maniatis, *et al.* (2001)	T1DM	None	7 to 23 years
Tsui, *et al.* (2001)	T1DM	None	18 to 60 years
DeVries, *et al.* (2002)	T1DM	≤ 0.20 nmol/l (if ≤ 30 years) ≤ 0.05 nmol/l (if ≤ 40 years)	18 to 70 years
Linn, *et al.* (2003)	T1DM	Negative C-peptide excluded	18 to 40 years
Jennings, *et al.* (1991)	T2DM	None	42 to 65 years
Raskin, *et al.* (2003)	T2DM	>0.2 nmol/l	55.1 ± 10.2(CSII) 56.0 ± 8.18(MDI)

Literature has been published since CMS's last decision memorandum exploring new concepts about the pathophysiology, diagnosis and treatment of diabetes. Defining diabetes as the result of long-lasting, immune-mediated destruction of pancreatic beta cells, Batstra and colleagues (2001) noted "autoantibodies originating from this process can be applied in the diagnosis and clinical discrimination of autoimmune diabetes as well as in the prediction of this disease." Over 85% of recently diagnosed patients with T1DM and only about 3.5% of patients with T2DM are said to be positive for beta cell autoantibodies. The most significant of these are islet cell antibodies (ICA), which were first described in T1DM in 1974, followed by later discovery of insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD) autoantibodies and insulinoma antigen (IA2) autoantibodies. According to Batstra's review, GAD and to a lesser degree ICA autoantibodies can be utilized "for the differential diagnosis of diabetes in adult patients and have a better predictive value than biochemical (C-peptide, HbA1c) or clinical parameters (age of diagnosis, BMI).[35]

On behalf of the Immunology of Diabetes Society, Greenbaum and Harrison also proposed that subjects in standardizing protocols for intervention trials in newly diagnosed T1DM should have at least one of the above four islet autoantibodies. These authors also clarified that although up to 10% of patients presenting with clinical T1DM are antibody negative and 10 to 15% of patients with clinical T2DM are autoantibody positive, autoantibody measurements remain the best indication that diabetes is immune-mediated and that the presence of one or more islet autoantibodies (i.e., GAD, IAA, IA2 or ICA) is a sufficient criterion for study enrollment.[36]

Other recent evidence regarding C-peptide as a surrogate outcome measure has been published since CMS's 2001 memorandum. For example, beta cell function in newly diagnosed T1DM was recently reported as a "measurable outcome that likewise predicts long-term clinical status." At an American Diabetes Association workshop held in October 2001, participants concluded that: "Measurement of C-peptide under standardized conditions provides a sensitive, well accepted, and clinically validated assessment of beta cell function. C-peptide measurement is the most suitable primary outcome for clinical trials of therapies aimed at preserving or improving endogenous insulin secretion in type 1 diabetes patients." Participants further noted "relatively low variability and high reproducibility of C-peptide measurements make the assay suitable for precisely assessing the durability of a beta cell effect over long periods of time."[37]

New articles have also quantified the prevalence of T2DM and need for additional study of CSII in the target Medicare population. As calculated from a 5% nationally representative random sample of claims from beneficiaries aged $\geq$ 65 years in the 1999 Medicare Standard Analytic Files, 94.8% of elderly diabetic patients identified had T2DM and only 5.2% had T1DM. Furthermore, it has been estimated that 96% of all Medicare beneficiaries with T2DM have at least one other chronic condition and 46% of all Medicare beneficiaries $\geq$ 65 years with T2DM have $\geq$ 5 comorbid conditions. The most prevalent comorbid conditions among these Medicare T2DM patients are hypertension (66%), lipid disorders (36%), coronary atherosclerosis (33%), congestive heart failure (23%) and cardiac dysrhythmias (19%).[38] Despite this health burden for elderly T2DM patients, a recent review of insulin pump therapy observed that: 1) Outcome data are "almost non-existent for use in type 2 diabetes"; 2) "There have been no large-scale randomized, controlled trials examining the use of external insulin pumps in patients with type 2 diabetes"; and 3) "When considering both cost-effectiveness and risk-benefit, there are no compelling reasons to widely use insulin pumps in patients with type 2 diabetes at this time."[39]

As introduced in the background section, C-peptide levels can be useful in the assessment of beta cell reserve. There are, however, limits to their use in patients with hyperglycemia or renal disease.

Investigators observed that the beta cell response in both animal and human subjects could be recovered with improvements in glycemic control. The restoration of euglycemia or near euglycemia was more important than the specific modality (pharmacological intervention, diet, weight loss) used to achieve glycemic control.[40,41,42,43,44,45,46,47,48,49] In an attempt to identify the pathophysiology, Brunzell, *et al.* (1976) delineated impairment of the first phase insulin response (insulin release within 10 minutes) of beta cells in T2DM patients with fasting glucose levels >6.4 mmol/l.[50] Pfeifer, *et al.* (1981) demonstrated an impaired insulin response to non-glucose stimuli in diabetic subjects.[51] Dimitriadis, *et al*. (1985) and Goodner, *et al.* (1969) observed abnormal islet cell responses to short-term infusion of glucose in normal volunteers.[52,53] Islet cell impairment after glucose infusion was also observed in animal studies of cats by Dohan and Lukens (1948), dogs by Imamura, *et al.* (1988), and rats by Leahy, *et al*. (1987).[54,55,56] This is supported by pancreatic fibrosis and islet cell disarray observed in rats after 3 months of hyperglycemia (>10 mmol/l)[57] and the impaired insulin secretion by islet cells incubated for 1 week in glucose (16.7 mmol/l versus 5.6 mmol/l).[58]

Although the endocrinology community has generally accepted this concept of “glucose toxicity”, there were contradictory studies, which showed that insulin secretion in non-diabetic subjects improved in response to hyperglycemia.[59,60,61,62,63,64] The duration of hyperglycemia was relatively short and/or the magnitude of hyperglycemia relatively mild (<7.2 mmol/l) in many of these studies. These methodological shortcomings were addressed by Boden, *et a*l. (1996) in a 4-day triphasic study in normal volunteers.[65] Patients were assessed at baseline with a euglycemic clamp using 6,6-$^{2}H_2$ glucose for glucose disposal studies. Patients were randomized to either euglycemic (5 mmol/l) or hyperglycemic (~ 8.8 or 12.6 mmol/l) clamps lasting 68 hours. Glucose levels were then normalized for all patients in another euglycemic clamp. C-peptide levels were low at baseline, but were elevated for all 3 days of the ~ 8.8 mmol/l hyperglycemic clamp. Insulin levels were even more elevated after initiation of the ~ 12.6 mmol/l hyperglycemic clamp, but decreased markedly over the 3 days. Insulin secretion was blunted by 35% ($p < 0.05$). There was a concomitant decrease in insulin clearance, but it only partially compensated for the impairment in secretion as demonstrated by the incremental decreases in the mean daily glucose infusion rates over time in the ~ 12.6 mmol/l hyperglycemic clamp cohort. For only the ~ 12 mmol/l cohort was insulin mediated glucose disposal lower (36%) and basal glucose disposal higher (55%) during the terminal euglycemic clamp. These findings suggested an increase in peripheral insulin resistance and residual hyperstimulation of the islet cells induced by the recent hyperglycemia. Additional C-peptide studies were not reported so it is not known how long normalization of beta cell secretion would take.

Renal function also affects C-peptide levels. Prolonged insulin activity in patients with renal impairment has been studied primarily in patients with end-stage disease.[66,67,68,69] Hyperinsulinemia was observed in 29 patients with a variety of renal diseases and a mean glomerular filtration rate of 25ml/min.[70] Pharmacokinetic studies conducted for insulin products also support decreased rates of insulin clearance in such patients (see product inserts). The magnitude of any effect from renal impairment is likely to be larger with C-peptide because of its longer serum residence time.[71] The effect of renal function on insulin and C-peptide has been most systematically studied in untreated hypertensive, non-diabetic patients (N = 321 patients, N = 92 normotensive controls) by Sechi, *et al.* (2002) using oral glucose tolerance testing.[72] Fasting insulin, fasting C-peptide, and area-under-the-curve$(AUC)_{insulin}$ levels did not differ by renal function until the creatinine clearance was <50 ml/min. At that level of dysfunction, fasting insulin levels increased by ~ 20%, fasting C-peptide levels increased by ~ 100%, and $AUC_{insulin}$ increased by ~ 60%.

Current Health Plan Policy

In the submitted summary analysis for this reconsideration, the requestor stated it was unaware of any commercial payer policy in the United States currently implementing C-peptide testing as a criterion for insulin pump use. Additionally, in a May 26, 2004 follow-up letter to CMS, the requestor estimated 400 Medicare patients a year failed to meet the C-peptide criterion and that of those patients approximately 15 to 25% (that is, 60 to 100 patients) were unable to continue CSII once enrolling in Medicare because of the C-peptide testing requirement.

Aetna's (2004) Clinical Policy Bulletin #0161 explicitly requires documentation of a C-peptide level <0.5 ng/mL for determination of the medical necessity of external insulin infusion pumps for T1DM patients who have been on a pump prior to enrollment in Aetna and have a documented frequency of glucose self-testing an average of at least 4 times per day during the month prior to Aetna enrollment.

Matching that reported by the 2003 NICE technology appraisal on CSII, Aetna also concluded that “there is inadequate evidence of the effectiveness of continuous subcutaneous insulin infusion pumps for persons with type 2 diabetes (formerly known as non-insulin dependent diabetes mellitus (NIDDM)). Subcutaneous insulin infusion pumps are considered experimental and investigational for all persons with type 2 diabetes, including insulin-requiring type 2 diabetics.”

In their bulletin’s introductory paragraph, Aetna noted these conclusions were reached “based upon a review of currently available clinical information, including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors.”[73]

4. Medicare Coverage Advisory Committee (MCAC)

This issue was not referred to the MCAC.

5. Evidence-Based Guidelines

CMS was unable to identify any guidelines for the use of CSII or insulin pumps in T2DM. A 1999 Blue Cross Blue Shield of California “Treatment Guideline for T2DM” submitted by the requestor is not hyperlinked or referenced in the peer-reviewed literature. Its bibliography for “elements of intensive insulin management” referenced only the DCCT’s study of T1DM, and the document provided no evidence-based guidelines for the use of insulin pumps in T2DM.

6. Professional Society Position Statements

CMS received one position statement, but no formal professional society guidelines, from the American Association of Clinical Endocrinologists (AACE). The AACE requested that CMS remove the C-peptide criterion from the NCD for insulin pump therapy but provided no new articles or guidelines. The AACE additionally commented: “Outside of the C-peptide test, we agree the Medicare clinical criteria for insulin pump coverage is consistent with clinical practice, payer policies and professional society recommendations.” This AACE letter and all other comments received in the 30-day comment period are hyperlinked for viewing on our tracking sheet for this reconsideration at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=41.

Members of the AACE Intensive Insulin Management Task Force and representatives of Medtronic MiniMed also met with CMS on July 13, 2004 to discuss the AACE’s intent to specifically design and publish practice guidelines for intensive insulin management. A first draft outline of the categories of evidence to be examined by AACE task force included: 1) evidence that intensified insulin delivery may be necessary for T1DM, T2DM, Pediatrics, Obstetrics and Geriatrics, as well as any potentially contraindicated populations; 2) insulin delivery protocols, including basal-bolus concept, MDI, CSII pumps and insulin mixtures; 3) evidence that protocols achieve normoglycemia, target A1C levels and improved outcomes; 4) targets for intensified insulin delivery including pre-prandial, post-prandial and continuous glucose monitoring; 5) diabetes education programs; 6) role of the endocrinologist and rationale for referrals for hyperglycemia; 7) barriers to insulin therapy including low literacy, indigent and transplants; and 8) pharmaceutical issues.

An ADA position statement on CSII, originally approved in 1985 and most recently re-published in the January 2004 supplement of *Diabetes Care*, was last formally reviewed and/or revised in 2002.[74] This one page position statement generally addresses intensive diabetes management but does not provide formal guidelines or otherwise detail the appropriate use of CSII in T2DM.

The American Academy of Family Physicians (2004), while not providing an official position statement, did note in its home study self-assessment program that if the diagnosis between T1DM and T2DM remains uncertain: “A fasting insulin level, a C-peptide level or a beta cell autoantibody measurement usually can remove any diagnostic uncertainty (Table 11)”.[75]

7. Expert Opinion

CMS received 124 comments from practitioners, including physicians, nurse practitioners, registered nurses, certified diabetes educators and registered dieticians, who favored the modification or removal of Medicare’s C-peptide testing requirement.

- One university endocrinologist, who is both a clinical research unit and fellowship training program director, stressed that he did not support widespread use of insulin pumps for the treatment of T2DM, specifically "the unjustified widespread use of insulin pumps for patients with true insulin resistant T2DM." He considered CSII to be "an unnecessarily expensive form of treatment" which should be reserved only for those T2DM patients for whom there were strict but well-designed and fair criteria to allow use in those "few situations" where special needs or circumstances exist.
- Another physician wrote that he had no question that "if studied properly the few number of type 2 patients who truly require insulin pumps to properly control their disease would save the system money" due to fewer short and long-term complications.

All comments are hyperlinked and available for viewing on the tracking sheet for this decision memorandum at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=41.

8. Public Comments

CMS received 7 comments from patients and family members, who favored the modification or removal of Medicare's C-peptide testing requirement. These comments are hyperlinked and available for viewing on the tracking sheet for this decision memorandum at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=41.

All position statements, expert opinion and public comments were carefully reviewed and considered in CMS's analysis and conclusions.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

The purpose of this decision memorandum is not to reassess the effectiveness of CSII in the management of insulinopenic diabetic patients. Rather, this decision memorandum responds to the request to remove or modify CMS's C-peptide testing requirement for identifying those Medicare patients who are insulinopenic. Our 1999 and 2001 decision memoranda recognized that T1DM patients are insulinopenic and, if accurately diagnosed, are eligible for intensive insulin management with CSII provided that all remaining Medicare coverage criteria for insulin pump use are met. CMS likewise recognized that a subgroup of T2DM patients may become insulinopenic and could benefit from CSII provided that all remaining Medicare coverage criteria are met. However, CMS limited the use of CSII for both groups of patients to those diabetics whose insulinopenia was diagnosed by absent or decreased C-peptide levels. Therefore, CMS's basic criterion for the use of CSII pump therapy requires an accurate diagnosis of T1DM or, lacking that, an accurate diagnosis of insulinopenia. This decision memorandum reviews the evidence for removing, replacing or modifying the use of fasting C-peptide levels as the diagnostic criterion for both T1DM and insulinopenic T2DM.

Most individuals with T1DM are diagnosed clinically during an acute episode of hyperglycemia and ketosis. They are typically children, adolescents or young adults. It is unusual for T1DM to be diagnosed initially in the Medicare elderly population. It is sometimes difficult, however, to determine whether a Medicare beneficiary on insulin for a number of years has T1DM or has T2DM requiring insulin augmentation. The presence of beta cell autoantibodies indicates immune-mediated disease and autoantibody measurement is recognized by diabetologists as the best indicator for diagnosing immune-mediated T1DM. Beta cell autoantibody testing similarly enhances identification of a slowly progressive form of T1DM named type 1.5 diabetes or latent autoimmune diabetes in adults (LADA), which can be misdiagnosed as T2DM. Therefore, as an alternative to C-peptide testing, CMS will also allow a positive beta cell autoantibody test to be an adequate diagnostic criterion for CSII use provided that all remaining coverage criteria detailed in the updated Medicare NCD Manual are met.

CMS's review of the literature did not identify any consistent means of identifying diabetic patients for inclusion in CSII pump therapy trials. Most of the literature reviewed either specified that only T1DM patients were included without carefully describing how that diagnosis was made or, in several instances, used C-peptide levels as an inclusion (or exclusion) criterion for studies of CSII and/or MDI in which C-peptide secretion was absent or poor. Studies have also begun to evaluate the benefit of intensive insulin management with CSII in T1DM and T2DM patients exhibiting some residual beta cell function. Generally, those patients had C-peptide levels that met CMS's current criteria.

Two studies evaluated CSII in T2DM patients. Jennings, *et al.'s* (1991) randomized trial excluded patients who had features suggesting T1DM, such as those with islet cell antibody (ICA), but otherwise did not describe specific means for diagnosing either T1DM or T2DM.[76] Raskin, *et al.* (2003) included patients with a fasting C-peptide at baseline $\geq$ 0.2 nmol/ml who had T2DM for $\geq$ 2 years duration and treatment with insulin for $\geq$ 6 months, but this study also did not precisely describe how T1DM or T2DM patients were diagnosed.[77]

Thus, we are unable to identify any consensus that the use of CSII in patients who are not beta cell autoantibody positive should be limited only to those who meet defined C-peptide criteria. However, many studies used that criteria and others did not define how they determined patients to be T1DM or insulinopenic. There was, however, a general consensus in the literature, in our review of the NICE Technology Assessment, in Aetna's policy and from expert opinion that the use of CSII is rarely indicated in T2DM and that strict criteria should be used for eligibility. We believe that our current requirement of a low C-peptide should continue to be a selection criterion for those patients who are not beta cell autoantibody positive.

The concept of “glucose toxicity” is relatively well accepted among endocrinologists.[78] Elevated glucose levels directly suppress beta cell function and also appear to induce peripheral tissue insulin resistance. Tissue culture data and anatomic pathology support this concept of “glucose toxicity”.[79],[80] Insulin secretion is low in islet cells incubated in high levels of glucose, and islet cells become fibrotic. Cross-sectional studies support this.[81],[82] Poorly controlled diabetic patients and animals often have low fasting and/or stimulated C-peptide or insulin levels. First phase insulin responses are also impaired. Observational and intervention studies assessing the islet cell response to the reversal of hyperglycemia by a variety of means support this. [83],[84],[85],[86],[87],[88],[89],[90],[91],[92] The data demonstrating actual hyperglycemic induction of islet cell impairment are more problematic. Mild hyperglycemia for a short period of time may induce hyperinsulinemia. The most definitive study by Boden, *et al.* (1996) demonstrated beta cell dysfunction after only 3 days of a sustained serum glucose of ~ 12.6 mmol/l.[93] The defect was not immediately reversible, but we have no good data delineating the time-to-reversal. Nor do we know whether lower levels of hyperglycemia, if sustained for longer periods of time, would result in beta cell dysfunction. However, it is clear from this data that an accurate measurement of C-peptide depends on serum glucose being sufficiently controlled so as to avoid glucose toxicity and an erroneously low C-peptide level. Since Boden, *et al*. demonstrated the toxicity at a sustained serum glucose of ~ 12.6 mmol/l, we believe the serum glucose should be maintained below that level prior to measuring the C-peptide. That level corresponds to a fasting glucose level of ~ 225 mg/dL. We will add that requirement to our NCD. Although the stimulated C-peptide and the $AUC_{C\text{-}peptide}$ are believed to contribute to the assessment of insulin reserve[94],[95],[96],[97], there are insufficient data on the impact of hyperglycemia on these parameters to satisfy current documentation requirements.

Although clinical experience has long suggested that insulin doses need to be reduced in the setting of renal impairment, there are only limited data assessing the effect of renal clearance on C-peptide and insulin levels. Many of the studies have pharmacodynamic endpoints, are small, include patients with a variety of renal disorders, include patients only with end-stage renal disease, include patients with diabetes, and/or include patients on confounding drugs such as ACE inhibitors or thiazide diuretics. By contrast, Sechi’s (2002) relatively large study included patients with a spectrum of renal clearance, and was not confounded by drug therapy or diabetes.[98] Its results are concordant with the other studies and demonstrate that fasting C-peptide levels increased by 100% when creatinine clearance levels drop below 50 ml/min. In order to not preclude the potential benefits of CSII in patients who may have this artifactually elevated C-peptide, we will alter our C-peptide requirement for patients who are not beta cell autoantibody positive and have decreased renal function to less than or equal to 200% of the lower limit of normal of the laboratory’s measurement method.

In attempting to determine whether any studies examined by CMS can be generalized to the Medicare population, only DeVries, *et al’s.* (2002) trial had an age range (18 to 70 years) that included some elderly Medicare beneficiaries, and that trial used C-peptide levels as an inclusion criterion to define T1DM.[99]

As originally discussed in the “Analysis of Scientific Data on CSII for Type I Diabetes” section of CMS’s 1999 decision memorandum, an important criticism of studies relating to Medicare coverage has been that the 1993 DCCT, as well as the majority of other studies, excluded elderly patients.[100] In that landmark study of T1DM, enrollment was limited to patients ranging from 13 to 39 years, as well as patients without hypertension, hypercholesterolemia, severe diabetic complications or other comorbidities. The enrolled DCCT subjects are not representative of the target Medicare population but, as noted in CMS’s 1999 decision memorandum, it seemed reasonable based upon the consistency of study results to extrapolate available data to Medicare beneficiaries.[101]

However, in the DCCT's (1993) discussion section, the authors cautioned that the risk-benefit ratio for intensive therapy may be less favorable "…in patients with advanced complications, such as end-stage renal disease or cardiovascular or cerebrovascular disease." Furthermore, the DCCT studied only T1DM and noted: "If the main conclusions of this trial with regard to the benefits of reducing glycemia are extended to patients with NIDDM T2DM, careful regard for age, capabilities, and coexisting diseases will be necessary. We therefore advise caution in the use of therapies other than diet that are aimed at achieving euglycemia in patients with NIDDM T2DM."[102] While tempered by findings of fewer, later microvascular complications for T2DM in the later United Kingdom Prospective Diabetes Study (UKPDS)[103], the DCCT's concern about the external validity of its young, highly motivated patient population again underscores the necessity for new randomized trials that can be generalized to the Medicare population.

This lack of information on the elderly coupled with potential increased risks and problems with the devices demonstrated by frequent FDA bulletins all support a restrictive policy for those Medicare beneficiaries who are not beta cell autoantibody positive.

In summary, if diabetic Medicare patients are not beta cell autoantibody positive, CMS believes it is appropriate to require that these patients meet an updated C-peptide testing requirement. The updated (2004) C-peptide testing requirement will include new provisions for patients with renal insufficiency and a concurrently obtained fasting glucose $\leq$ 225 mg/dL.

IX. Conclusions

CMS, therefore, updates its Medicare coverage criteria for insulin pump therapy to facilitate the improved diagnosis and treatment of diabetic patients benefiting from CSII, as well as to encourage further research into intensive insulin management of diabetes in the context of approved clinical trials:

- CMS has determined that the evidence is adequate to conclude that continuous subcutaneous insulin infusion (CSII) is reasonable and necessary for treatment of diabetic patients: 1) who are documented (once) to either meet the updated fasting C-peptide testing requirement or be beta cell autoantibody positive; and 2) who satisfy the remaining criteria for insulin pump therapy detailed in the Medicare National Coverage Determinations Manual (Medicare NCD Manual 280.14, Section A.5).
- CMS has determined that fasting C-peptide levels will only be considered valid with a documented, concurrently obtained fasting glucose $\leq$ 225 mg/dL. Insulinopenia may be documented by a fasting C-peptide level that is less than or equal to 110 percent of the lower limit of normal of the laboratory's measurement method. Alternatively, for patients with renal insufficiency and documented creatinine clearance (actual or calculated from age, weight and serum creatinine) $\leq$ 50 ml/minute, insulinopenia may be documented by a fasting C-peptide level that is less than or equal to 200 percent of the lower limit of normal of the laboratory's measurement method.
- CMS will continue to allow coverage of all other uses of CSII in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201) or as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1).

CMS is requesting public comments on this proposed decision memorandum pursuant to Section 731 of the Medicare Modernization Act.[104] After considering the public comments, we will issue a final decision memorandum.

CMS additionally looks forward to future trials defining evidence-based criteria for CSII utilizing serum markers and other laboratory measures endorsed by professional society guidelines to examine the aforementioned health outcomes of interest in both T1DM and T2DM. We will also closely watch for publication of the AACE task force's evidence-based guidelines, especially those sections dealing with the geriatric use of intensified insulin delivery systems and populations in which intensified insulin protocols may be contraindicated.

Medicare NCD Manual 280.14 (formerly CIM 60-14) Section A.5

280.14 – Infusion Pumps

(Rev. 1, 10-03-03)

CIM 60-14

“5 - Continuous subcutaneous insulin infusion pumps (CSII) - Effective for Services Performed On or after 4/1/2000.

An external infusion pump and related drugs/supplies are covered as medically necessary in the home setting in the following situation:

Treatment of diabetes

In order to be covered, patients must meet criterion a or b:

Criterion a

The patient has completed a comprehensive diabetes education program, and has been on a program of multiple daily injections of insulin (i.e. at least 3 injections per day), with frequent self-adjustments of insulin dose for at least 6 months prior to initiation of the insulin pump, and has documented frequency of glucose self-testing an average of at least 4 times per day during the 2 months prior to initiation of the insulin pump, and meets one or more of the following criteria while on the multiple daily injection regimen:

1. Glycosylated hemoglobin level (HbAlc) >7.0 percent
2. History of recurring hypoglycemia
3. Wide fluctuations in blood glucose before mealtime
4. Dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dl
5. History of severe glycemic excursions

Criterion b

1. The patient with diabetes has been on a pump prior to enrollment in Medicare and has documented frequency of glucose self-testing an average of at least 4 times per day during the month prior to Medicare enrollment.

Diabetes needs to be documented by a fasting C-peptide level that is less than or equal to 110 percent of the lower limit of normal of the laboratory's measurement method. Effective for Services Performed on or after January 1, 2002.

Continued coverage of the insulin pump would require that the patient has been seen and evaluated by the treating physician at least every three months.

The pump must be ordered by and follow-up care of the patient must be managed by a physician who manages multiple patients with CSII and who works closely with a team including nurses, diabetes educators, and dietitians who are knowledgeable in the use of CSII."

42 CFR 405.201

[Code of Federal Regulations]
[Title 42, Volume 2]
[Revised as of October 1, 2003]
From the U.S. Government Printing Office via GPO Access
[CITE: 42CFR405.201]

[Page 68-69]

“TITLE 42PUBLIC HEALTH

CHAPTER IVCENTERS FOR MEDICARE & MEDICAID SERVICES, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 405FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED—

Table of Contents

Subpart BMedical Services Coverage Decisions That Relate to Health Care Technology

Sec. 405.201 Scope of subpart and definitions.

Authority: Secs. 1102, 1862 and 1871 of the Social Security Act as amended (42 U.S.C.1302, 1395y, and 1395hh).

Source: 60 FR 48423, Sept. 19, 1995, unless otherwise noted.

(a) Scope. This subpart establishes that

(1) CMS uses the FDA categorization of a device as a factor in making Medicare coverage decisions; and

(2) CMS may consider for Medicare coverage certain devices with an FDA-approved investigational device exemption (IDE) that have been categorized as non-experimental/investigational (Category B).

(b) Definitions. As used in this subpart

Class I refers to devices for which the general controls of the Food, Drug, and Cosmetic Act, such as adherence to good manufacturing practice regulations, are sufficient to provide a reasonable assurance of safety and effectiveness.

Class II refers to devices that, in addition to general controls, require special controls, such as performance standards or postmarket surveillance, to provide a reasonable assurance of safety and effectiveness.

Class III refers to devices that cannot be classified into Class I or Class II because insufficient information exists to

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determine that either special or general controls would provide reasonable assurance of safety and effectiveness. Class III devices require premarket approval.

Contractors refers to carriers, fiscal intermediaries, and other entities that contract with CMS to review and adjudicate claims for Medicare services.

Experimental/investigational (Category A) device refers to an innovative device believed to be in Class III for which “absolute risk” of the device type has not been established (that is, initial questions of safety and effectiveness have not been resolved and the FDA is unsure whether the device type can be safe and effective).

IDE stands for investigational device exemption. An FDA-approved IDE application permits a device, which would otherwise be subject to marketing clearance, to be shipped lawfully for the purpose of conducting a clinical trial in accordance with 21 U.S.C. 360j(g) and 21 CFR parts 812 and 813.

Non-experimental/investigational (Category B) device refers to a device believed to be in Class I or Class II, or a device believed to be in Class III for which the incremental risk is the primary risk in question (that is, underlying questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type.

PMA stands for “premarket approval” and refers to a marketing application for a Class III device, which includes all information submitted with or incorporated by reference in the application in accordance with 21 U.S.C. 360e and 360j and 21 CFR 814.3(e).

Sponsor refers to a person or entity that initiates, but does not conduct, an investigation under an IDE.”

Medicare NCD Manual 310.1 (formerly CIM 30-1)

310.1 - Routine Costs in Clinical Trials

(Rev. 1, 10-03-03)

CIM 30-1

“Effective for items and services furnished on or after September 19, 2000, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials. All other Medicare rules apply.

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in either the experimental or the control arms of a clinical trial except:

- The investigational item or service, itself;
- Items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service - in particular, for the diagnosis or treatment of complications.

This policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies or the regulations on category B investigational device exemptions (IDE) found in 42 CFR 405.201 - 405.215, 411.15, and 411.406. For information about local medical review policies (LMRPs), refer to http://www.lmrp.net/, a searchable database of Medicare contractors' local policies."

Appendix A: General Methodological Principles of Study Design

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits. The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes, and we are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

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[1] http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h1enr.txt.pdf

[2] Mayfield 1998

[3] American Diabetes Association (ADA) 2004a

[4] DeFronzo 1997

[5] Turner, *et al.* 1997

[6] UKPDS 1998

[7] Takeda, *et al*. 2002

[8] Bennett 1989

[9] Boden, *et al.* 1996

[10]http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=40

[11] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=41

[12]http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=40

[13] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=41

[14] According to the FDA, recalls are “actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. A Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.” Additional information regarding FDA recalls is available at http://www.fda.gov/oc/po/firmrecalls/recall_defin.html and http://www.fda.gov/cdrh/recalls/.

[15] http://www.fda.gov/cdrh/recalls/recall-030204.html

[16] http://www.fda.gov/cdrh/recalls/recall-061702.html

[17]http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=40

[18] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=41

[19] http://www.nice.org.uk/pdf/57_Insulin_pumps_fullguidance.pdf

[20] Pickup, *et al.* 2002

[21] Weissberg-Benchell, *et al.* 2003

[22] DCCT 1986

[23] DCCT 1993

[24] DCCT 1998

[25] Hanaire-Broutin, *et al.* 2000

[26] Or diagnosed at or before age 40 years with a C-peptide level $\leq$ 0.05 nmol/l and glucose level $\geq$ 7.0 mmol/l

[27] DeVries, *et al.* 2002

[28] Linn, *et al.* 2003

[29] Raskin, *et al.* 2003

[30] Jennings, *et al.* 1991

[31] Bode, *et al.* 1996

[32] Boland, *et al.* 1999

[33] Maniatis, *et al.* 2001

[34] Tsui, *et al.* 2001

[35] Batstra, *et al.* 2001

[36] Greenbaum and Harrison 2003

[37] Palmer, *et al*. 2004

[38] Niefeld, *et al.* 2003

[39] Kirk 2003

[40] Boden, *et al.* 1983

[41] Ferner, *et al.* 1988

[42] Gumbiner, *et al.* 1990

[43] Hecht, *et al.* 1973

[44] Juhl, *et al.* 2001

[45] Kosaka *et al.* 1980

[46] Savage, *et al.* 1975

[47] Turner *et al.* 1976

[48] Unger, *et al.* 1985

[49] Wolffenbuttel, *et al.* 1992

[50] Brunzell, *et al.* 1976

[51] Pfeifer, *et al.* 1981

[52] Dimitriadis, *et al*. 1985

[53] Goodner, *et al.* 1969

[54] Dohan and Lukens 1948

[55] Imamura, *et al.* 1988

[56] Leahy, *et al*. 1987

[57] Clark, *et al.* 1982

[58] Eizirik, *et al.* 1992

[59] Flax, *et al.* 1991

[60] Kahn, *et al.* 1992

[61] Laury, *et al*. 1991

[62] Porte, *et al.* 1969

[63] Thibault, *et al.* 1993

[64] Ward, *et al.* 1984

[65] Boden, *et al.* 1996

[66] Alvestrand, *et al.* 1997

[67] DeFronzo, *et al.* 1978

[68] Horton, *et al.* 1968

[69] Westrevelt 1968

[70] Eidemak, *et al.* 1995

[71] Kjems, *et al.* 2000

[72] Sechi, *et al.* 2002

[73] http://www.aetna.com/cpb/data/PrtCPBA0161.html

[74] ADA 2004b

[75] Perry and Jain 2004

[76] Jennings, *et al.* 1991

[77] Raskin, *et al.* 2003

[78] DeFronzo 1997

[79] Eizirik, *et al.* 1992

[80] Clark, *et al.* 1982

[81] Brunzell, *et al.* 1976

[82] Pfeifer, *et al.* 1981

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[91] Unger, *et al.* 1985

[92] Wolffenbutel, *et al.* 1992

[93] Boden, *et al.* 1996

[94] Isomaa, *et al.* 1999

[95] Lee, *et al.* 1996

[96] Lee, *et al.* 1999

[97] Palmer, *et al.* 2004

[98] Sechi, *et al.* 2002

[99] DeVries, *et al.* 2002

[100] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=40

[101] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=40

[102] DCCT 1993

[103] UKPDS 1998

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